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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,896	07/14/2003	Paul G. Ahlquist	960296.00096	7353

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
12/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/618,896	AHLQUIST ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-32* is/are pending in the application.

4a) Of the above claim(s) *21-25 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-31-08 has been entered.

Applicants' amendment filed 10-31-08 has been entered. Claims 26 and 27 have been amended. Claims 31 and 32 have been added. Claims 21-32 are pending. Claims 26, 27, 31 and 32 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 26 and 27 read on using a delta9 fatty acid desaturase enzyme derived from various organisms, such as humans, rats, mice, canine, feline, sheep, cows, horses, monkeys, whales, other mammals, insects, birds, fish etc. The specification only discusses delta9 fatty acid

desaturase enzyme encoded by OLE1 gene in yeast. A search of OLE1 gene in the art only results in the OLE1 gene of Histoplasma capsulatum (a dimorphic pathogenic fungus) and OLE1 gene of yeast Saccharomyces cerevisiae at the time of the invention, i.e. 6-12-97.

The claims encompass a genus of numerous different delta9 fatty acid desaturase enzymes derived from various mammalian species, such as humans, rats, mice, canine, feline, sheep, cows, horses, monkeys, whales, and other mammals etc., and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features that contribute to the biological function of various delta9 fatty acid desaturase enzymes. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the discussion of the yeast OLE1 gene or enzyme in the present application is insufficient to describe the genus.

Applicants cite reference Thiede et al., 1986 and Ntambi et al., 1988, and argue that the mouse and rat delta9 fatty acid desaturase were known in the art and mammalian delta9 fatty acid desaturases were known to functionally replace yeast OLE1 gene (Stukey et al., 1990, Exhibit A). It should be noted that there are at least 5,000 species of mammal and the disclosure of mouse and rat delta9 fatty acid desaturase homologs is NOT sufficient to represent those at least 5,000 species of mammals. The cited reference Stukey reports that "[i]solation and

characterization of fatty acid desaturase enzymes has proved difficult due to their extraordinary hydrophobic nature and tight association with membranes. Although fatty acid desaturation was first described using the yeast delta9 desaturase system, only animal delta9 enzymes have been successfully purified to homogeneity (5, 6). At a genetic level, only the DNA sequence for the rat liver and mouse adipocyte genes have been reported and analyzed (7, 8)" (e.g. p. 20144, right column, 1st full paragraph). The animal delta9 enzymes that have been successfully purified to homogeneity as discussed by Stukey are rat and chicken stearoyl CoA desaturases, and the mouse and rat cDNA sequence encoding the stearoyl CoA desaturase have been isolated. Only the rat stearoyl CoA desaturase has been found to functionally replace the yeast delta9 fatty acid desaturase in yeast (e.g. abstract, reference Stukey). Whether numerous different mammalian species have similar metabolic mechanism of fatty acid desaturation as that of yeast is unclear and whether those numerous different mammalian species have delta9 fatty acid desaturase remain to be seen. There is no evidence of record that shows the presence of various mammalian delta9 fatty acid desaturases and whether they have the same function as the yeast delta9 fatty acid desaturase other than the rat stearoyl CoA desaturase.

Therefore, the limited information provided in the present invention is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the genus of numerous different delta9 fatty acid desaturase enzymes derived from various mammalian species. Thus, it is concluded that the written description requirement is not satisfied for the use of the genus of numerous different delta9 fatty acid desaturase enzymes derived from various mammalian species as claimed.

Applicants cite references Thiede, Ntambi and Stukey, and argue that applicants are not required to have possession of all the delta9 fatty acid desaturase enzymes encompassed by the claims. The native biological function of the delta9 homolog other than their role as a delta9 fatty acid desaturase is not important or necessary to understand for one to have possession of the present invention. Mammalian delta9 fatty acid desaturases were known to functionally replace yeast OLE1 gene (e.g. amendment, p. 5-6). This is not found persuasive because of the reasons set forth above.

4. Claims 26, 27, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for evaluating a substance as a brome mosaic virus (BMV) RNA antiviral agent by using yeast delta9 fatty acid desaturase, does not reasonably provide enablement for evaluating a substance as positive strand RNA antiviral agent by using a yeast OLE1 desaturase or mammalian delta9 fatty acid desaturase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the

inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 26 and 27 are drawn to a method of evaluating a substance as a positive strand RNA antiviral agent comprising exposing a substance to a yeast or mammalian delta9 fatty acid desaturase enzyme and evaluating the effect of the substance on the enzyme, wherein decrease in stability or inhibition of activity indicates that the substance is an antiviral agent against positive strand RNA virus. Claims 31 and 32 are drawn to a method of evaluating a substance as a positive strand RNA antiviral agent comprising exposing a substance to a yeast OLE1 desaturase enzyme and evaluating the effect of the substance on the enzyme, wherein decrease in stability or inhibition of activity indicates that the substance is an antiviral agent against positive strand RNA virus.

The specification discloses that brome mosaic virus (BMV) is a positive-strand RNA virus and the use of yeast Saccharomyces cerevisiae for virus replication studies (p. 2, 2nd paragraph). Ole1 protein is the desaturase that converts SFAs to UFAs (p. 49, lines 1-2). "BMV RNA replication did not require the Ole1 protein but rather required UFA levels well above those required for cell growth" (p. 47, 1st paragraph). "BMV RNA replication is strongly

dependent on UFA levels in vivo. When UFA was limited, ER-associated RNA replication was blocked after 1a and 2a membrane association and RNA3 template recognition and stabilization, but before negative-strand RNA synthesis. The ability to use ole1w mutation to block RNA replication at this stage should help to elucidate the early events in initiating RNA synthesis. Dependence of BMV RNA replication on UFA levels in particular implies a requirement for host membrane fluidity" (p. 51, 2nd paragraph).

The claims encompass using various yeast and mammalian delta9 fatty acid desaturases (OLE1 proteins) for evaluating a substance as a positive strand RNA antiviral agent by exposing a substance to the OLE1 proteins, wherein decrease in stability or inhibition of activity indicates that the substance is an antiviral agent against positive strand RNA virus.

As discussed above under 35 U.S.C. 112 first paragraph, written description requirement, the claims encompass a genus of numerous different delta9 fatty acid desaturase enzymes derived from various mammalian species, such as humans, rats, mice, canine, feline, sheep, cows, horses, monkeys, whales, and other mammals etc., and the specification fails to provide the structural features that contribute to the biological function of various delta9 fatty acid desaturase enzymes (OLE1 proteins). Applicants do NOT have possession of various mammalian delta9 fatty acid desaturase enzymes. Absent such possession, one skilled in the art would not know how to use the various mammalian delta9 fatty acid desaturases to practice the claimed invention, and would require undue experimentation to practice over the full scope of the invention claimed.

The specification fails to provide adequate guidance and evidence for the whether decrease in stability or inhibition of activity of various mammalian delta9 fatty acid desaturase or

yeast OLE1 protein would be indicative of an antiviral agent against various positive strand RNA viruses. The specification fails to provide adequate guidance and evidence for whether various mammalian delta9 fatty acid desaturase, other than rat stearoyl CoA desaturase as disclosed by Stukey, would have the same activity as yeast OLE1 protein to generate unsaturated fatty acid via same mechanism as yeast OLE1 protein, and a lack of unsaturated fatty acid would inhibit positive strand RNA virus replication as the case of BMV RNA virus.

It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and

"Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The biological functions of various mammalian delta9 fatty acid desaturases were unpredictable at the time of the invention. Various mammalian delta9 fatty acid desaturases could have different biological functions and there is no evidence of record that shows those different mammalian delta9 fatty acid desaturases would have the same activity as yeast OLE1 protein to generate unsaturated fatty acid via same mechanism as yeast OLE1 protein, and a lack of unsaturated fatty acid would inhibit positive strand RNA virus replication as the case of BMV RNA virus. Absent such guidance, one skilled in the art at the time of the invention would not know whether a substance effecting a decrease in stability or inhibition of activity of those mammalian delta9 fatty acid desaturases would be indicative of said substance as an antiviral agent against positive strand RNA viruses.

Further, there are numerous different types of positive strand RNA viruses, for example, Allexivirus, Astrovirus, avian nephritis virus, Barnavirus, Alfamovirus, Bronovirus, Cucumovirus, Oleavirus, Lagovirus, Norovirus, Sapovirus, Capillovirus, Carlavirus, Flavivirus, Foveavirus, Furovirus, Hepatitis E-like virus, Pecluvirus, Pomovirus, Potexvirus, Tobamovirus, and Vitivirus etc., and viral infection caused by those different viruses vary morphologically, physiologically and pathologically. The mechanisms of viral infection and the strategy of antiviral therapy for different viral infections would vary depending on the type of viral infection. Thus, a substance identified via its effect in decreasing stability or inhibiting activity of an OLE1 protein maybe a possible antiviral agent for a particular viral infection but said

substance would not necessarily be a possible antiviral agent for various other viral infections. There is no evidence of record that shows a decrease in stability or inhibition of activity of various mammalian delta9 fatty acid desaturase or yeast OLE1 protein would be indicative of an antiviral agent against various positive strand RNA viruses.

In addition, a search of state of the art of positive strand RNA virus and delta9 fatty acid desaturase results in only two literatures (post-filing) published by the group of instant invention's inventor. There is no report of a correlation between the delta9 fatty acid desaturase and a positive strand RNA virus. There is no evidence that shows a decrease in stability or inhibition of activity of a delta9 fatty acid desaturase would be indicative of an antiviral agent against various positive strand RNA viruses.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of skill which is high, the amount of experimentation required, and the breadth of the claims.

Applicants argue that positive strand RNA replication is strongly dependent on UFA levels and modulating composition of membrane helps to identify useful antiviral agents. There are substantial evidences that OLE1 homologs from yeast, mammals etc. have equivalent biological function and are functionally interchangeable in providing essential delta9 fatty acid desaturase functions. Delta9 fatty acid desaturases by definition share the common biosynthetic function of modifying fatty acids by insertion of a double bond at a specific position. Any

hypothetical possibility that such enzymes might have other functions is irrelevant (amendment, p. 6-7). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph. The only mammalian delta9 fatty acid desaturase homolog of yeast OLE1 that has interchangeable function with yeast OLE1 is the rat stearoyl CoA desaturase disclosed by Stukey. As discussed above, applicants do NOT have possession of various mammalian delta9 fatty acid desaturase enzymes. Absent such possession, one skilled in the art would not know how to use the various mammalian delta9 fatty acid desaturases to practice the claimed invention, and would require undue experimentation to practice over the full scope of the invention claimed. Various mammalian delta9 fatty acid desaturases could have different biological functions and there is no evidence of record that shows those different mammalian delta9 fatty acid desaturases would have the same activity as yeast OLE1 protein to generate unsaturated fatty acid via same mechanism as yeast OLE1 protein, and a lack of unsaturated fatty acid would inhibit positive strand RNA virus replication as the case of BMV RNA virus. Further, there are numerous different types of positive strand RNA viruses, and viral infections caused by those different viruses vary morphologically, physiologically and pathologically. The mechanisms of viral infection and the strategy of antiviral therapy for different viral infections would vary depending on the type of viral infection. Thus, a substance identified via its effect in decreasing stability or inhibiting activity of an OLE1 protein maybe a possible antiviral agent for a particular viral infection but said substance would not necessarily be a possible antiviral agent for various other viral infections. There is no evidence of record that shows a decrease in stability or inhibition of activity of various mammalian delta9 fatty acid desaturase or yeast

OLE1 protein would be indicative of an antiviral agent against various positive strand RNA viruses.

Applicants argue that only partial inhibition of delta9 fatty acid desaturase activity is required to inhibit viral RNA replication and total inhibition is not required. In both mammals and yeast, it was well established that synthesis of all UFAs proceeds through the action of delta9 fatty acid desaturases as first step (Stukey et al., 1990 and references therein) (amendment, p. 7). This is not found persuasive because of the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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